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Infant event-related potentials to speech are associated with prelinguistic development

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ABSTRACT

Neural auditory processing and prelinguistic communication build the foundation for later language development, but how these two are associated is not well known. The current study investigated how neural speech processing is associated with the level and development of prelinguistic skills in 102 infants. We recorded event-related potentials (ERPs) in 6-months-olds to assess the neural detection of a pseudoword (obligatory responses), as well as the neural discrimination of changes in the pseudoword (mismatch responses, MMRs). Prelinguistic skills were assessed at 6 and 12 months of age with a parental questionnaire (Infant-Toddler Checklist). The association between the ERPs and prelinguistic skills was examined using latent change score models, a method specifically constructed for longitudinal analyses and explicitly modeling intra-individual change. The results show that a large obligatory P1 at 6 months of age predicted strong improvement in prelinguistic skills between 6 and 12 months of age. The MMR to a frequency change was associated with the concurrent level of prelinguistic skills, but not with the improvement of the skills. Overall, our results highlight the strong association between ERPs and prelinguistic skills, possibly offering opportunities for early detection of atypical linguistic and communicative development.

1. Introduction

Learning oral and written language requires efficient auditory processing of speech (Gervain, 2015). The first observable step of language development is the emergence of prelinguistic skills, that is, a variety of mainly nonverbal means of communication such as babbling, pointing, and making eye contact (Spencer, 2011; Watt et al., 2006). Studies on the association between neural auditory processing and prelinguistic skills are scarce. To fill this gap and advance the understanding of early communicative development, we investigated these associations longitudinally in 6–12-month-old infants.

Recording auditory event-related potentials (ERPs) derived from the electric signal of the brain (electroencephalography [EEG]; Kuhl, 2010; Thierry, 2005) is an optimal method for studying young children, as it is noninvasive, easy to administer, and requires no active participation (Hoehl and Wahl, 2012; Thierry, 2005). Sounds elicit the obligatory P1 and N2 responses, both robust and well-defined ERPs (Choudhury and Benasich, 2011; Kushnerenko et al., 2002a). In infants and young children, the positively-displaced P1 reflects stimulus detection and registration, whereas the negatively-displaced N2 reflects acoustic sound-feature processing (Čeponiene et al., 2008; Čeponiené et al., 2005). The mismatch negativity (MMN) or mismatch response (MMR), in turn, is a pre-attentive response reflecting the discrimination of a discrepant (deviant) stimulus in a stream of repeating stimuli (standard stimulus; Bartha-Doering et al., 2015; Näätänen et al., 2007). The MMN amplitude, obtained by subtracting the standard-stimulus response from the deviant-stimulus response, has a negative polarity at frontal electrode sites in adults, but in infants positively-displaced MMRs are common (Choudhury and Benasich, 2011; Kushnerenko et al., 2002b). The focus in the present work will be in ERP amplitudes as a measure of neural auditory processing, although also other features of ERPs have been investigated (e.g. for associations between ERP latencies and

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language skills see Cantiani et al., 2016; Riva et al., 2018). Previous studies imply that auditory ERPs are concurrently associated with oral and written language skills (for reviews see Hämäläinen et al., 2013; Kujala and Leminen, 2017). The P1 and the N2 have, for instance, been associated with word-naming speed and phonological skills in 6-year--olds (Kuuluvainen et al., 2016), and with phonological and reading skills in school-aged children (Hämäläinen et al., 2018). MMRs have been associated with vocabulary in 5-year-olds (Linnavalli et al., 2017), and to phonological and reading skills in school-aged children (Bonte et al., 2007; Hämäläinen et al., 2018).

ERP amplitudes measured at a young age also show associations with future oral and written language skills, and it has been suggested that they could be predictive markers of language (Kujala and Leminen, 2017; van der Leij et al., 2013). For example, a large N2 in 6-month-olds was found to be associated with strong subsequent language skills (complex tone stimuli and oral language skills at 3–4 years in Choudhury and Benasich, 2011; speech stimuli and reading speed at 14 years in Lohvansuu et al., 2018). Furthermore, large P1-like responses in newborns were associated with good phonological skills in toddlers and good reading skills in second-graders (sinusoidal tone stimuli, Leppänen et al., 2010), and large P1s at gestational week 40 were associated with an advanced neurodevelopmental level at 24 months of age (complex tone stimuli, neurodevelopmental level assessed with Bayley Scales of Infant Development, Fellman et al., 2004). Associations between MMRs or discriminatory N2 (N2 to a deviant stimulus), and subsequent language skills have also been found (e.g. Cantiani et al., 2016; Leppänen et al., 2010; but see Lohvansuu et al., 2018). A large N2 to a frequency and/or duration deviant at 6 months was associated with better subsequent language skills even though the MMR was not (language measured at 3–4 years in Choudhury and Benasich, 2011; at 20 months in Cantiani et al., 2016; complex tone stimuli in both). Furthermore, the MMR to a frequency change in newborns was associated with phonological skills in toddlers and reading skills in second-graders (sinusoidal tone stimuli, Leppänen et al., 2010), and the MMR to a stress pattern change at 5 months of age was associated with vocabulary in toddlerhood (speech stimuli, Weber et al., 2005). Only those two-month-old infants who showed an MMR to a consonant change were fluent readers as second-graders (speech stimuli, van Zuijen et al., 2013). Finally, a large discriminatory response to a consonant change at 2 months of age was found to be associated with good communication skills at 12 months of age and strong language at 24 months of age (equiprobable stimulus design with speech stimuli; Maitre et al., 2013). Longitudinal associations between language skills and change-related neural measures other than the MMR/discriminatory N2 (e.g. neural oscillations and vocabulary, Cantiani et al., 2019; source-resolved P3 and vocabulary, Piazza et al., 2016; complex tone stimuli in both) have also been reported.

Many fundamental principles of human communication, such as intentionality and the engagement in joint attention, are learned during the prelinguistic phase (Feldman, 2007; Tomasello et al., 2007; Watt et al., 2006), and prelinguistic skills are associated with later language skills (Cadime et al., 2017; Lohmander et al., 2017; Määttä et al., 2016; Murillo et al., 2018; Paavola et al., 2005). Although both efficient neural auditory processing and good prelinguistic skills are vital for early communicative development (Kuhl, 2010; Snowling and Melby-Lervåg, 2016), only two studies have, to our knowledge, investigated their associations (Fellman et al., 2004; Maitre et al., 2013). In these studies, prelinguistic skills were not measured *per se*, but rather as a part of an index targeting a broad range of skills, and both studies had prematurely born children as their participants (Fellman et al., 2004; Maitre et al., 2013).

The aim of our study was to examine how infants' neural speech processing is associated with the concurrent level and the subsequent development of prelinguistic skills. We assessed neural auditory processing using ERPs (P1, N2, and MMR), and prelinguistic skills using a standardized questionnaire. ERPs were measured at 6 months of age and prelinguistic skills at 6 and 12 months of age. Our hypotheses were: Large amplitudes of the P1, the N2, and MMRs are associated with a) a high level of prelinguistic skills at 6 months of age and b) a strong improvement in prelinguistic skills between 6 and 12 months of age.

To test the hypotheses, we used latent change score models (LCS models), a subtype of structural equation models (SEM). In LCS models intra-individual change is explicitly modeled, which is optimal for investigating longitudinal effects (Kievit et al., 2018; Petscher et al., 2016). Participants with data missing at some time points can be included in LCS models (Allison, 2003; Enders, 2001; Savalei and Bentler, 2005), and measurement error can be taken into account when the model is estimated (McArdle, 2009; Westfall and Yarkoni, 2016). These characteristics give the LCS model an advantage over traditional methods, such as correlations or ANOVA, especially when handling longitudinal data (Gueorguieva and Krystal, 2004; McArdle, 2009).

Table 1
The age of the infants for EEG and questionnaire data.

Variable	N (girls)	Mean	SD	Min	Max
Age, EEG	102 (38)	6.11	0.30	5.45	6.57
Age, ITC6	98 (34)	6.24	0.33	5.55	7.00
Age, ITC12	88 (31)	12.02	0.33	11.40	13.11

Note. Age is expressed in months in the table, but in all analyses, we used age in days. ITC6 = prelinguistic skills measured with the Infant–Toddler Checklist (Laakso et al., 2011; Wetherby and Prizant, 2002) at 6 months of age; ITC12 = Infant–Toddler Checklist at 12 months of age. The numbers of infants across variables differ since we did not have questionnaire data from all infants at both ages.

2. Methods

2.1. Data

This study includes a subsample of the infants participating in the DyslexiaBaby (2014–present) project (described in Thiede et al., 2019; Virtala and Partanen, 2018). The families were recruited with advertisements in Finnish maternity clinics, project webpages, and Facebook, through local learning disorder associations as well as through media, and event appearances. For the current study, we collected EEG and questionnaire data at 6 months of age, and questionnaire data at 12 months of age (Table 1). Parents gave written informed consent when the infant was enrolled in the study at birth. The study was conducted in accordance with the declaration of Helsinki and the Ethics Committee for Gynaecology and Obstetrics, Pediatrics, and Psychiatry (Hospital District of Helsinki and Uusimaa) approved the study protocol.

2.2. Participants

The original sample consisted of 211 healthy full-term infants who had passed a hearing screening done routinely at Finnish hospitals (detailed description of inclusion criteria in Thiede et al., 2019). Infants were excluded from the analysis due to the following reasons: failure to meet inclusion criteria (13 infants), families withdrawing from the study (2), failure to schedule the EEG recording at 6-month follow-up (56), restlessness during the EEG recording (8), EEG data quality issues (27; see section 2.6.1), or missing ITC questionnaires at both the 6- and the 12-month time point (3; see section 2.5). The final sample consisted of 102 infants (38 girls). The DyslexiaBaby sample was selected to be overrepresentative of infants with a heightened risk of developing language difficulties due to parental dyslexia, and 82 of the infants of the current study were infants with at least one parent with dyslexia. Of these 82 infants, 52 participated in a music listening intervention between 0 and 6 months of age (preliminarily described in Virtala and Partanen, 2018). The sample also included 20 infants with no familial risk of language difficulties. In the present study, we utilized the complete sample and collapsed across all groups while controlling for parental dyslexia and intervention group in analyses.

2.3. Stimuli

The stimuli were Finnish bisyllabic pseudowords uttered by a female native Finnish speaker, first used by Pakarinen et al. (2014; see Thiede et al., 2019 for the original description of the present stimuli and paradigm). The stimuli were presented in an oddball paradigm with a repeating standard stimulus and occasional duration, frequency, and vowel identity deviants. The paradigm also contained very rarely-presented non-linguistic novel sounds, the data for which not being included in the analyses of the current study.

Deviant stimuli were constructed by editing the second syllable of the standard /tata/ with Adobe Audition CS6 (version 5.0; Adobe Systems Inc.) and Praat (version 5.4.01; Boersma and Weenik, 2013). Root mean square normalization was used to match the sound intensity levels of the standard and the deviants. The duration deviant was constructed by lengthening the duration of the second syllable from 71 ms to 158 ms by copying and pasting the center of the last /a/. The frequency deviant was constructed by lifting the F0-level of the second syllable from 175 Hz to 225 Hz, and the vowel deviant was constructed by replacing the second syllable with a separately recorded syllable /to/ with the same F0-level and duration as the original syllable. The stimuli were presented in four blocks each containing 472 stimuli, of which on average 70.1 % were standard stimuli and 25.3 % deviants (remaining 4.6 % novel sounds). Each deviant type was presented with a probability of approximately 8.5 %. The duration of each test block was seven minutes and the onset time between the stimuli (stimulus-onset asynchrony, SOA) was 900 ± 50 ms. The SOA randomly alternated between 850, 860, 870, …, 940, 950 ms, minimizing expectancy effects related to the predictability of the stimulus onset. Every block started with 4 standards, and every deviant and novel stimulus was followed by a standard; otherwise, the presentation order was randomized.

2.4. Data acquisition and procedure

EEG data were recorded with 18 active electrodes placed on an EEG cap (ActiCap; Brain Products GmbH) according to the international 10/20 system. We used the QuickAmp amplifier (version 10.08.14; Brain Products GmbH) and the recording software BrainVision Recorder (version 1.20.0801; Brain Products GmbH). The data were sampled at a rate of 500 Hz and lowpass filtered online with 100 Hz as cutoff frequency. During the recordings, the data were referenced to the average of all electrodes. EEG recordings were carried out at Jorvi Hospital of Helsinki University Hospital (n = 87) and at a laboratory of the University of Jyväskylä (n = 15), both in Finland. The same models of equipment and recording protocol were used at both recording sites. The infants were awake and sitting in their parent's lap during the measurements, which took approximately one and a half hour with preparations included. A research assistant or nurse entertained the infants during the measurement by silently interacting with them or showing toys. We used the software Presentation 17.2 (Neurobehavioural Systems Ltd., Berkeley, CA, USA) and a Genelec speaker for presenting the stimuli. The speaker was placed behind the infant's head and the stimulus intensity at the infant's head was approximately 65 dB (sound pressure level, SPL). The background noise of the room was approximately 40 dB (SPL).

2.5. Prelinguistic skills

Prelinguistic skills were assessed with the Finnish version of the standardized parental questionnaire Infant–Toddler Checklist (ITC) in the Communication and Symbolic Behavior Scales Developmental Profile (Laakso et al., 2011; Wetherby and Prizant, 2002) at 6 and 12 months of age. Questionnaires that were returned when the infant was older than 220 days (mean rounded to closest tenth + 30 days) at the 6-month time point or older than 400 days at the 12-month time point were regarded as missing. ITC has three subscales, which have been shown to have moderate to good internal consistency (Eadie et al., 2010). The Social subscale consists of 13 questions (max 26 scores) concerning emotion expression, communication attempts, eye gaze, and gestures. The Speech subscale consists of five questions (max 14 scores) concerning babbling and attempts to form words. The Symbolic subscale consists of six questions (max 17 scores) concerning speech comprehension, play, and symbolic use of objects. In the current study, we used the raw scores for each subscale. All subscales showed moderate correlation (see Tables 2a and 2b) at both 6 and 12 months of age. The correlation coefficients indicated a stronger correlation between the Social and Symbolic scales than between the Social and the Speech scales, or between the Symbolic and the Speech scales. These differences were significant only in the 12-months data (test for equality of two correlation coefficients, $p < 0.05$).

Table 2a
Correlation between ITC subscales at 6 months of age.

	Soc6	Speech6	Symb6
Soc6	1.00		
Speech6	.37	1.00	
Symb6	.41	.25	1.00

Note. Soc = Social subscale, Speech = Speech subscale, Symb = Symbolic subscale, 6 = assessed at 6 months of age. N = 98.

Table 2b
Correlation between ITC subscales at 12 months of age.

	Soc12	Speech12	Symb12
Soc12	1.00		
Speech12	.37	1.00	
Symb12	.58	.26	1.00

Note. Soc = Social subscale, Speech = Speech subscale, Symb = Symbolic subscale 12 = assessed at 12 months of age. N = 88.

2.6. Analysis

2.6.1. EEG preprocessing

We first visually inspected the data using BESA Research (version 6.0; BESA GmbH, 2012) and identified electrodes that had continuous noise, hereinafter referred to as bad data/electrode. Peripheral electrodes (FP1, FP2, F7, F8, Oz[1]) with bad data were excluded from further analyses, whereas central electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with bad data were interpolated during the data preprocessing (max two electrodes interpolated per block, adjacent electrodes interpolated in approximately 10 % of all blocks). The preprocessing was done with MATLAB (Release 2016b; MathWorks, 2016) as well as MATLAB toolboxes EEGLAB (version 14.0.0; Swartz Center for Computational Neuroscience [SCCN], Delorme and Makeig, 2004) and ERPLAB (Lopez-Calderon and Luck, 2014). The data were first filtered with half-amplitude frequencies of 0.5 Hz and 25 Hz using the *pop_eegfiltnew* function in EEGlab (version 14.0.0, SCCN), and re-referenced to the average of two mastoid electrodes (RM, LM) and two posterior scalp electrodes (P7, P8). After this, the continuous data were segmented into −100–840 ms epochs around stimulus onset and binned according to stimulus type. The epochs were baseline-corrected using a baseline from −100 to 0 ms relative to stimulus onset. In order to reduce eye-movement related artifacts, epochs with an absolute amplitude exceeding ±120 μV in electrodes close to the eyes (Fp1, Fp2) were

[1] Oz was excluded for all infants as it was not an electrode of interest and was bad in the majority of recordings.

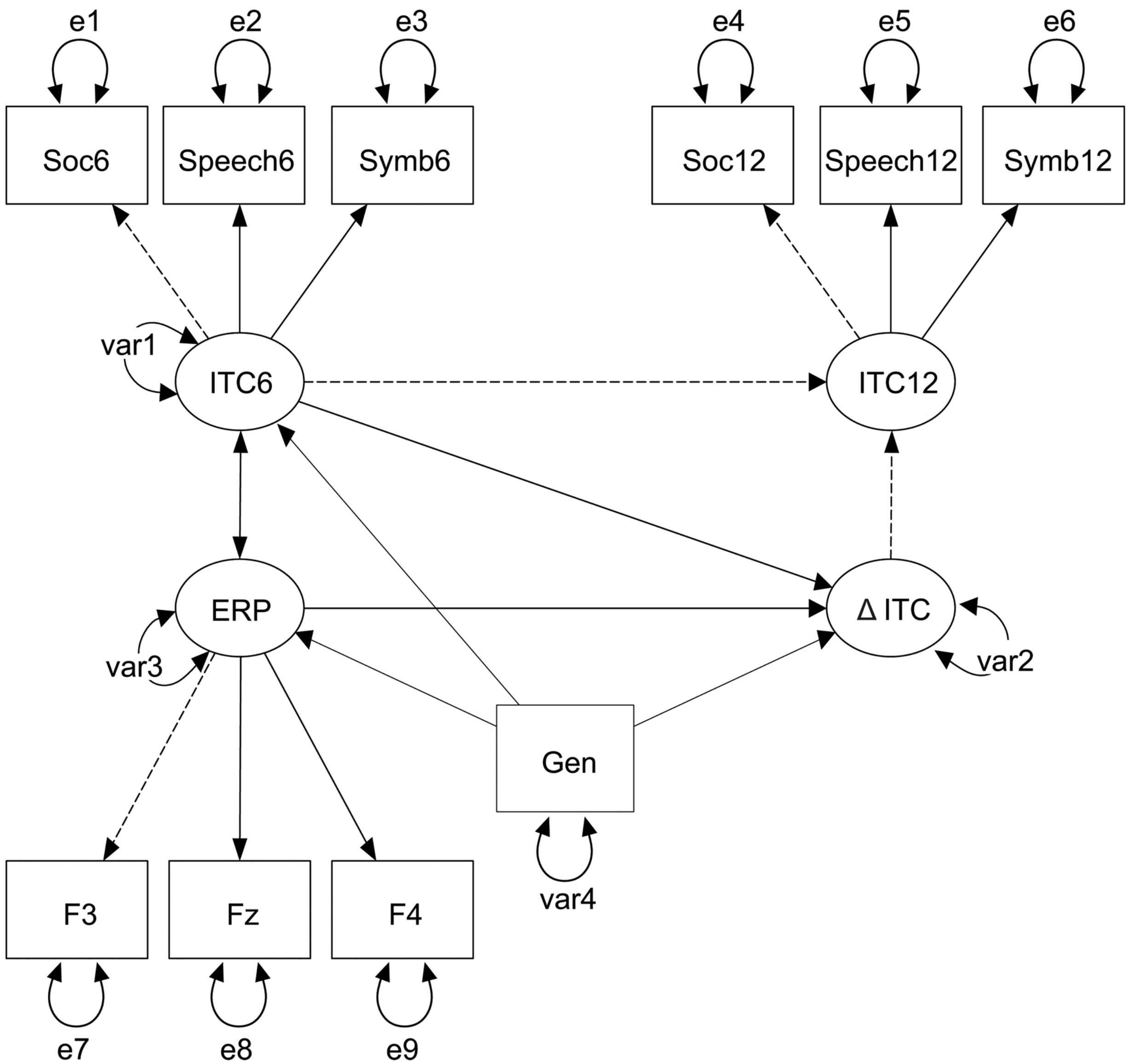

Fig. 1. A schematic of the main LCS model. Latent variables are plotted as ovals and measured variables as rectangles. Single-headed arrows represent loadings and regressions, while double-headed arrows represent variances and covariances. Dashed lines represent paths with unstandardized estimates fixed to one. ITC = latent for the Infant–Toddler Checklist [prelinguistic skills], Δ ITC = change in ITC, ERP = latent for the event-related potential (ERP) response being tested, Soc = Social subscale, Speech = Speech subscale, Symb = Symbolic subscale, F3/Fz/F4 = amplitude of the ERP response on electrodes F3/Fz/F4. Numbers after ITC, Soc, Speech, and Symb represent the age (in months) at which they were assessed. Based on the results of the preliminary correlation analyses, we tested two main models: one model for the P1 response and one for the MMR response to a frequency deviant.

rejected. Thereafter, epochs with amplitudes exceeding ±3 SD from the mean for a single electrode or across electrodes were rejected using the *pop_jointprob* function in EEGlab (version 14.0.0, SCCN) and epochs with large linear drifts (maximum absolute slope 180 μV; minimum $R^2 = 0.3$) were rejected using the *pop_rejtrend* function in EEGLAB (version 14.0.0, SCCN).

Data of infants with less than 40 accepted epochs for more than one stimulus type were excluded from further analysis (see section 2.2). The mean number of accepted epochs per infant was 320 epochs for the standard stimulus and 68 epochs for each deviant stimulus. The data from the two recording sites (Helsinki and Jyväskylä) were of comparable quality as measured by the number of accepted trials: the number of accepted epochs did not statistically differ between data recorded in Helsinki vs. Jyväskylä (t test $p > 0.15$ for all stimulus types except for standards, for which there was a trend of more accepted epochs in the Jyväskylä data ($p = 0.076$). As our main analyses were within-subject comparisons we did not deem this trend of a difference to be relevant.

2.6.2. *Extracting ERPs*

ERP amplitudes for individual infants were extracted using the toolboxes EEGlab (version 14.0.0; Delorme and Makeig, 2004) and CBRUPlugin (version 2.0b; Makkonen, 2018) in MATLAB (Release 2018b; The MathWorks, Inc., Natick, Massachusetts, USA). We first averaged the data across all infants and three electrodes of interest (F3, Fz, and F4) for plotting. Obligatory responses (P1 and N2) were calculated from the standard stimulus waveform and MMRs for each deviant type were calculated from deviant-minus-standard waveforms. For the analyses of MMRs we re-applied the baseline correction to −100–0 ms prior to change onset instead of stimulus onset, resulting in a baseline correction window of 125–225 ms for the duration deviant (MMR_{dur}) and 80–180 ms for frequency (MMR_{freq}) and vowel identity (MMR_{vow}) deviants. Based on visual inspection and peak latencies calculated from the resulting waveforms, we extracted mean amplitudes for five time windows, reported in milliseconds after stimulus onset for standards and milliseconds after deviance onset for deviants: 143–193 ms for P1,

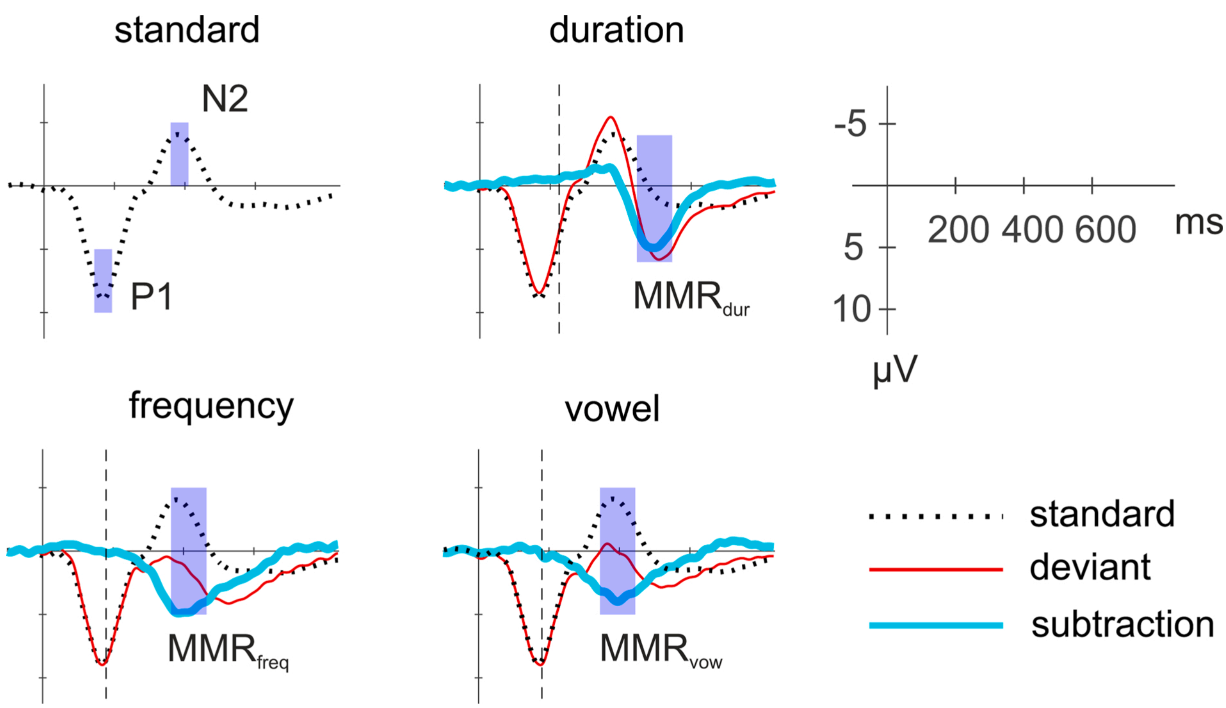

Fig. 2. The event-related potentials (ERPs, average of F3, Fz, F4) to standard stimulus and each deviant stimulus, and subtraction curves (standard-minus-deviant) for the deviants. Stimulus-change onset is marked with a dashed vertical line and the windows for ERP extraction with a violet box. For visual clarity, the baseline is set to −100–0 ms relative to stimulus onset for all waveforms even though we used a baseline of −100–0 ms relative to change onset for the mismatch responses (MMRs) in the analyses.

360–410 ms for N2, 221–321 ms for MMR_{dur}, 185–285 ms for MMR_{freq}, and 165–265 ms for MMR_{vow}. The data were separately extracted for all infants and all electrodes of interest (F3, Fz, and F4).

2.6.3. Statistical analysis

Associations between variables of interest were preliminarily explored using univariate Pearson correlations in Stata (Release 15; StataCorp LLC, 2017). The variables of interest were as follows: P1, N2, MMR_{dur}, MMR_{freq}, MMR_{vow}, ITC at 6 months of age (ITC6), ITC at 12 months of age (ITC12). For the exploratory analysis we used mean totals for ERPs (mean of electrodes F3, F4, and Fz) and ITC (mean of Social, Speech, and Symbolic subscales). As P1 and MMR_{freq} amplitudes were associated with ITC scores ($p < 0.05$, not corrected for multiple comparisons), we further examined them in the main LCS analyses. There were 72 infants with complete ITC data at both 6 and 12 months of age. The rest (30 infants) had a missing score in one or more subscales at the 6- or 12-months stage (one scale missing: n = 16, two scales missing: n = 5, three scales missing: n = 9). To ensure that the data were missing at random (MAR) as required for the estimation method used, we tested for covariate-dependent missingness (CDM), which is a special case of MAR (Li, 2013; Little, 1988). We added gender as a covariate since more girls than boys (Pearson $\chi2$ (df) = 6.85, $p = 0.01$) had missing ITC values. CDM was confirmed (Little's CDM test; $\chi2$(df) = 141 (168), $p = 0.94$) with gender as a covariate. It has been recommended that the covariates included in the CDM test should also be added to the model being estimated (Li, 2013; Little, 1995). We therefore added gender as a covariate to all models.

In the LCS analyses, we first modeled the latent structure of ITC at 6 and 12 months of age ($Model1_{itc6}$ and Model 1_{itc12}) to check that the data fitted the latent structure we were suggesting. We formed latent variables for both time points, ITC6 and ITC12, with the three ITC subscale scores (Social, Speech, and Symbolic subscale) as observed variables (Soc, Speech, and Symb, respectively). The scaling indicator (Soc) was fixed to one. Then we modeled the change in ITC between 6 and 12 months of age to check that the change was significant ($Model1_{behav}$). To create the latent change score, we first regressed ITC12 perfectly on ITC6, that is, fixed the regression weight between ITC6 and ITC12 to one. Then we defined the latent change score factor (ΔITC) as perfectly measured by ITC12, again by regressing ITC12 on ΔITC with a regression weight of one. The intercept and the variance of ITC12 were fixed to zero (Kievit et al., 2018; Petscher et al., 2016). Using this procedure, the latent change variable ΔITC captured the change between ITC at 6 and 12 months of age. We also regressed ΔITC on ITC6 in order to account for any possible effect of prelinguistic ability at the baseline measure at 6 months (ITC6) on the change in ITC over time. We examined measurement invariance between the observed variables measured at the two time points using the following stepwise approach: First, we estimated the latent factor loadings of the observed variables freely at both time points. Then we fixed the loadings of first the Speech subscale and then the Symbolic subscale to be the same across time points. The fit of the model decreased significantly when fixing the loadings of either of the subscales (see Supplement 1, Table S1 for model fit), indicating that measurement invariance could not be established. The loadings of the Speech subscale and the Symbolic subscale on the ITC latent were therefore freely estimated in all the reported models allowing the relation between the subscales and the latent variables to be different at the two time points.

To ensure that the latent structures of the selected ERP variables (P1 and MMR_{freq}) were valid, we constructed Model 1_{P1} and Model $1_{freq.}$ In these models, a latent variable (P1 or MMR_{freq}) was formed using the response amplitudes at electrodes F3, Fz, and F4 as observed variables (P1F3, P1Fz, P1F4, FreqF3, FreqF4, FreqF4). The scaling indicator (P1F3/FreqF3) was fixed to one. We then combined the behavioral change model (Model 1_{P1}) with each of the ERP models (Model 1_{P1} or Model 1_{freq}) to form two new models (Model 2_{p1} and Model 2_{freq}), one for each selected ERP (see Fig. 1 for a schematic of the models). In Model 2_{p1} we examined the association between P1 and ΔITC, and in Model 2_{freq} we did the same for the association between and MMR_{freq} and ΔITC. Gender was included as a controlling variable in all models mentioned above. Error terms and variances were freely estimated for all variables.

Table 3
Pearson correlations between mean values of variables of interest.

	P1	N2	MMR_{dur}	MMR_{freq}	MMR_{vow}
ITC6	.05	−.05	.01	.24*	.03
ITC12	.22*	−.10	.07	.29*	.16

Note. ITC6 = mean scores of the three subscales of the Infant-Toddler Checklist (ITC, prelinguistic skills) at 6 months of age; ITC12 = mean scores of the three subscales of ICT at 12 months of age; P1–MMR_{vow} = mean of the event-related potential (ERP) amplitude of electrodes F3, Fz, and F4. The values displayed are correlation coefficients. * = uncorrected $p < 0.05$.

Table 4
Model fits for all models.

	χ2 (df)	p	RMSEA [90 % CI]	CFI	TLI	SRMR
Model 1_{ITC6}	5.18 (4)	.270	.05 [.00–.16]	.96	.95	.06
Model 1_{ITC12}	0.28 (4)	.991	.00 [.00–.00]	1.00	1.16	.01
Model 1_{behav}	7.46 (16)	.963	.00 [.00–.00]	1.00	1.15	.06
Model 1_{p1}	4.81 (4)	.307	.05 [.00–.16]	1.00	1.00	.05
Model 1_{freq}	8.56 (4)	.073	.11 [.00–.20]	.98	.97	.05
Model 2_{p1}	37.24 (36)	.412	.02 [.00–.08]	1.00	1.00	.06
Model 2_{freq}	34.15 (36)	.557	.00 [.00–.07]	1.00	1.01	.07

Note. Model 1_{itc6} = latent structure for the Infant-Toddler Checklist (ITC, prelinguistic skills) at 6 months of age, Model 1_{itc12} = latent structure for the ITC at 12 months of age, Model 1_{behav} = latent structures for the ITC at 6 and 12 months of age, and change in ITC; Model 1_{p1} = latent structure for the P1 response; Model 1_{freq} = latent structure for the mismatch response for the frequency deviant; Model 2_{p1} = Model 1_{behav} + Model 1_{p1}; Model 2_{freq} = Model 1_{behav} + Model 1_{freq}. Gender included as a control variable in all models. RMSEA = root mean square error of approximation, CFI = comparative fit index, TLI = Tucker–Lewin index, SRMR = standardized root mean square residual.

To check the robustness of our results, we also constructed models controlling for parental dyslexia and intervention status. Intercepts were estimated for ITC6, ΔITC, and P1/ MMR_{freq}, and fixed to zero for observed variables.

The LCS models were fitted using the toolbox lavaan (Rosseel, 2012) in R (version 3.5.1; R Core Team, 2018). Multivariate normality was not established in the data, as indicated by the Doornik-Hansen test and the skewness marker of the Mardia test ($p < 0.05$), mainly due to non-normality in the ITC speech subscale at 6 and 12 months. To account for multivariate nonnormality we used robust standard errors (Huber, 1967) and scaled test statistics (Satorra and Bentler, 1994; Yuan and Bentler, 2000) for the maximum likelihood (ML) estimation of the model. We used the full information ML (FIML; Yuan and Bentler, 2000) to be able to include infants with ITC data missing for one time point. It has been shown that models can reliably be estimated using FIML when data measured at various time points are missing for some time point, but available for at least one time point (Allison, 2003; Shin, 2016). For data measured at only one time point, this is not an option and therefore complete data was required for ERP and control variables. Model fit was assessed with a combination of fit metrics (as suggested by e.g. Kievit et al., 2018; Marsh et al., 2004; Schermelleh-Engel et al., 2003). The fit metrics used were as follows: the likelihood of a significant difference between the expected and observed covariance matrix with the χ2 test (good fit: $p \geq .05$), comparative fit index (CFI; good fit $\geq .95$), Tucker–Lewis index (TLI; good fit $\geq .95$), the root mean square error of approximation (RMSEA; good fit $\leq .06$), and the standardized root mean square residual (SRMR; good fit $\leq .08$). The fit of the model was considered good if it was good in all the indices and acceptable if it was good in all but one of the five indices.

Table 5
Parameter estimates for the latent change score (LCS) Model 2_{p1}.

Latent variables	Unstandardized (SE)	Standardized	p
ITC6			
Soc6	*1.00*	*0.79*	
Speech6	0.25 (0.02)	0.36	≤.001
Symb6	0.38 (0.02)	0.57	≤.001
ITC12			
Soc12	*1.00*	*0.83*	
Speech12	0.34 (0.01)	0.40	≤.001
Symb12	0.49 (0.01)	0.66	≤.001
P1			
P1F3	*1.00*	*0.96*	
P1Fz	0.99 (0.01)	0.98	≤.001
P1F4	1.04 (0.02)	0.93	≤.001
ITC6 -> ITC12	*1.00*	*0.85*	
Δ ITC -> ITC12	*1.00*	*0.88*	
Regressions			
ITC 6 -> Δ ITC	−0.33 (0.24)	−0.32	.165
P1 -> Δ ITC	0.20 (0.10)	0.27	.044
Gender->ITC6	0.41 (0.75)	0.07	.581
Gender-> Δ ITC	−1.14 (0.71)	−0.19	.107
Gender -> P1	−1.41 (0.75)	−0.17	.059
Covariances			
ITC6 < -> P1	0.31 (0.87)	0.04	.723
Intercepts			
ITC6	9.88 (0.66)	4.26	≤.001
Δ ITC	10.95 (2.55)	4.56	≤.001
P1	9.44 (0.65)	2.90	≤.001
Gender	0.80 (0.04)	2.03	≤.001
Variances			
ITC6	5.37 (1.36)	1.00	≤.001
Δ ITC	4.42 (1.36)	0.77	≤.001
P1	10.28 (1.47)	0.97	≤.001
Gender	0.16 (0.02)	1.00	≤.001
Soc6	3.33 (1.12)	0.38	.003
Speech6	2.27 (0.31)	0.87	≤.001
Symb6	1.58 (0.28)	0.67	≤.001
Soc12	3.34 (1.28)	0.31	.009
Speech12	4.66 (0.63)	0.84	≤.001
Symb12	2.31 (0.36)	0.56	≤.001
P1F3	0.80 (0.22)	0.07	≤.001
P1Fz	0.51 (0.21)	0.05	.017
P1F4	1.90 (0.42)	0.14	≤.001

Note. The statistics of variables fixed to 1 are in italics. The statistics of variables fixed to zero (intercepts and variance of ITC12, and intercepts of observed variables) are omitted from the table. ITC = latent for Infant–Toddler Checklist [prelinguistic skills], Δ ITC = change in ITC, P1 = latent for P1, Soc = Social subscale, Speech = Speech subscale, Symb = Symbolic subscale, P1F3/P1Fz/P1F4 = amplitude of the P1 response on electrodes F3/Fz/F4, Gender = gender, girl as reference. Numbers after ITC, Soc, Speech, and Symb represent age in months.

3. Results

3.1. ERPs and preliminary correlations

The P1–N2 complex in response to the standard stimulus and the MMRs to the three deviants are illustrated in Fig. 2. The P1 amplitude and the ITC12 score, as well as the MMR_{freq} amplitude and the ITC6 and ITC12 score, were correlated (Table 3).

3.2. LCS models

Model 1_{ITC6} and Model 1_{ITC12} had good fits (Table 4), demonstrating that describing ITC as one latent factor indicated by the ITC subscales was appropriate at both time points. The fit of Model 1_{behav} was good

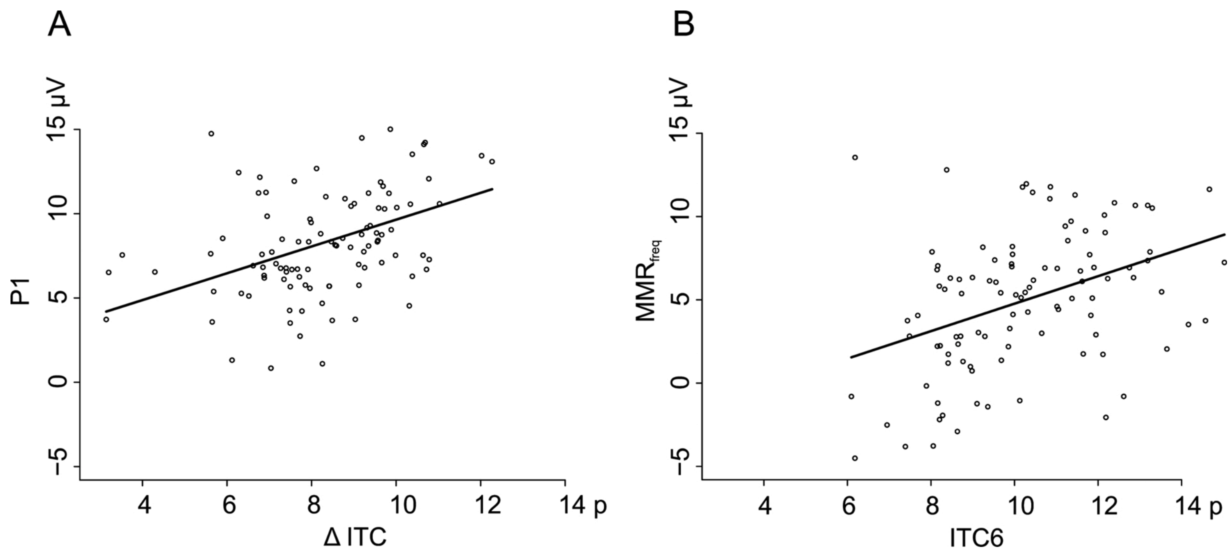

Fig. 3. Scatterplots showing the significant associations between the P1 response and the change in the Infant–Toddler Checklist (ITC, prelinguistic skills) (a), as well as between the mismatch response for the frequency deviant (MMR_{freq}) and the level of the ITC at 6 months of age (b).

(Table 4) and revealed a significant mean increase of 11.65 ITC scores between 6 and 12 months of age. The level of ITC at 6 months of age did not predict change in ITC, and gender did not predict the level or change of ITC ($p > 0.05$, Supplement 2, Table S2.1). Model 1_{p1} had a good fit and Model 1_{freq} had an acceptable fit (Table 4) suggesting that describing the components at the different electrodes as one latent factor was adequate for each of the two components. Gender did not predict the level of P1 or MMR_{freq} in Model 1_{p1} or Model 1_{freq} ($p > 0.05$, Supplement 2, Table S2.2 and S2.3).

The fits of the models estimating the association between prelinguistic skills and ERPs (Model 2_{p1} and Model 2_{freq}) were good (Table 4), and all estimated intercepts and variances significantly differed from zero. Model 2_{p1} revealed that a stronger P1 amplitude at 6 months predicted a larger change in ITC score between 6 and 12 months of age (Table 5, Fig. 3a). The level of ITC at 6 months of age did not covary with the P1 amplitude while there was a nonsignificant trend of a larger P1 in girls (Table 5). Controlling for parental dyslexia and intervention status did not modify the main results, even though there was an effect of a smaller P1 in infants with a parent with dyslexia (Supplement 3, Tables S3.1, S3.2, S3.4). Model 2_{freq} showed that the MMR_{freq} amplitude at 6 months was positively associated with the concurrent ITC score, but did not predict the change in the ITC score (Table 6, Fig. 3b). There was a nonsignificant trend of a larger change in ITC in girls compared to boys (Table 6). The results were the same when we controlled for parental dyslexia and intervention status, despite a nonsignificant trend of a smaller change in ITC in infants with a parent with dyslexia (Supplement 3, Tables S3.1, S3.3, S3.5).

4. Discussion

Efficient neural auditory processing and prelinguistic communication are foundations of future language skills, but their associations have, however, very scarcely been investigated. The present study determined whether the level and development of prelinguistic skills can be predicted by neural speech processing in infancy. The study was conducted with a large longitudinal sample and well-documented and established methods (auditory ERPs, Hoehl and Wahl, 2012; Thierry, 2005, and the parental questionnaire ITC, Laakso et al., 2011; Wetherby and Prizant, 2002), using a statistical approach specifically designed for modelling longitudinal effects (LCS, Kievit et al., 2018; Petscher et al., 2016). The results showed that a large P1 response to a repeating pseudoword measured at 6 months of age, predicted a strong improvement in prelinguistic skills between 6 and 12 months of age. This association was not explained by the level of prelinguistic skills at 6 months. The MMR elicited by a frequency change in a pseudoword (MMR_{freq}), was positively associated with the concurrent level of prelinguistic skills at 6 months, but not with the subsequent change in prelinguistic skills. The correlation analyses in the present study did not demonstrate associations between MMR_{dur}, MMR_{vow}, or N2 and prelinguistic skills, contrary to our hypothesis and previous results (e.g. Cantiani et al., 2016; Choudhury and Benasich, 2011; Lohvansuu et al., 2018; van Zuijen et al., 2013). As correlations were used mainly as a preliminary step, the following discussion will focus on the results of the LCS models.

Our results are in line with previous studies showing that large P1 responses (Cantiani et al., 2016; Fellman et al., 2004; Leppänen et al., 2010) and large MMRs or other change-related responses to frequency changes (Cantiani et al., 2019, 2016; Choudhury and Benasich, 2011; Leppänen et al., 2010) are associated with good language-related skills. In infants and young children, the P1 has been proposed to reflect the detection of and orienting to a sound (Čeponiene et al., 2008; Čeponiené et al., 2005; Ortiz-Mantilla et al., 2012). Following this line of thought, we suggest that in the current study a large P1 reflects strong orienting towards speech or auditory input, which may drive the association between P1 amplitude and prelinguistic development. Strong orienting towards speech and communication input is likely to enhance the learning of communication-relevant skills, such as turn-taking, joint attention, and word-object pairing (Feldman, 2007; Kuhl, 2010). Our results showed that MMR_{freq} was not associated with the change in prelinguistic skills from 6 to 12 months, suggesting that in these data MMR_{freq} did not predict the development of prelinguistic skills. The LCS model, however, showed a concurrent association between MMR_{freq} and ITC6, which implies that the MMR reflects some aspects of sensory-cognitive functions that are relevant for prelinguistic skills. The MMR shifts polarity during the first year of life (Cheng et al., 2015; He et al., 2007), and due to this, there probably is extensive individual variation in the polarity of the response at 6 months of age. The lack of an association between the prelinguistic development and the MMR could be a consequence of this unstable maturational stage of the infant MMR at 6 months, compared to the more robust P1 response to the repeating standard.

Most of the previous studies focused on oral or written language skills, while we studied prelinguistic skills. Prelinguistic and linguistic skills are closely related (Cadime et al., 2017; Lohmander et al., 2017;

Table 6
Parameter estimates for the latent change score (LCS) Model $2_{freq.}$

Latent variables	Unstandardized (SE)	Standardized	p
ITC6			
Soc6	*1.00*	*0.80*	
Speech6	0.25 (0.02)	0.37	≤.001
Symb6	0.38 (0.02)	0.57	≤.001
ITC12			
Soc12	*1.00*	*0.84*	
Speech12	0.34 (0.01)	0.39	≤.001
Symb12	0.49 (0.01)	0.66	≤.001
MMR_{freq}			
FreqF3	*1.00*	*0.88*	
FreqFz	0.93 (0.05)	0.92	≤.001
FreqF4	0.96 (0.05)	0.87	≤.001
ITC6 -> ITC12	*1.00*	*0.86*	
Δ ITC -> ITC12	*1.00*	*0.88*	
Regressions			
ITC 6 -> Δ ITC	−0.41 (0.25)	−0.41	.099
MMR_{freq} -> Δ ITC	0.14 (0.10)	0.26	.130
Gender->ITC6	0.41 (0.74)	0.07	.585
Gender-> Δ ITC	−1.35 (0.70)	−0.22	.055
Gender -> MMR_{freq}	0.76 (1.08)	0.07	.479
Covariances			
ITC6 < -> MMR_{freq}	3.23 (1.44)	0.32	.025
Intercepts			
ITC6	9.89 (0.66)	4.21	≤.001
Δ ITC	12.93 (2.45)	5.36	≤.001
MMR_{freq}	4.34 (0.96)	1.01	≤.001
Gender	0.80 (0.04)	2.03	≤.001
Variances			
ITC6	5.50 (1.38)	1.00	≤.001
Δ ITC	4.57 (1.19)	0.78	≤.001
MMR_{freq}	18.39 (2.58)	1.00	≤.001
Gender	0.16 (0.02)	1.00	≤.001
Soc6	3.14 (1.10)	0.36	.004
Speech6	2.25 (0.31)	0.87	≤.001
Symb6	1.63 (0.29)	0.67	≤.001
Soc12	3.24 (1.22)	0.30	0.008
Speech12	4.66 (0.63)	0.84	≤.001
Symb12	2.33 (0.35)	0.57	≤.001
FreqF3	5.42 (1.30)	0.23	≤.001
FreqFz	2.86 (1.18)	0.15	.015
FreqF4	5.69 (1.20)	0.25	≤.001

Note. The statistics of variables fixed to 1 are in italics. The statistics of variables fixed to zero (intercepts and variance of ITC12, and intercepts of observed variables) are omitted from the table. ITC = latent for Infant–Toddler Checklist [prelinguistic skills], Δ ITC = change in ITC, MMR_{freq} = latent for the MMR for the frequency deviant, Soc = Social subscale, Speech = Speech subscale, Symb = Symbolic subscale, FreqF3/FreqFz/FreqF4 = mean amplitude of MMR_{freq} on electrodes F3/Fz/F4, Gender = gender, girl as reference. Numbers after ITC, Soc, Speech, and Symb represent age in months.

Murillo et al., 2018; Paavola et al., 2005), but it is quite possible that different ERPs are associated with the level and development of prelinguistic as compared to linguistic skills. The investigations that best compare to our study in terms of the behavioral outcomes, assessed associations between ERPs and neurodevelopmental level in prematurely born children (Fellman et al., 2004; Maitre et al., 2013). These studies did not focus on prelinguistic skills but used broad indices including measurements of interaction and emerging language skills. The results were in line with those of ours, showing that a large P1 to a non-speech stimulus (Fellman et al., 2004) and discriminatory response to a change in a speech stimulus (Maitre et al., 2013) were associated with communication and language skills in toddlerhood.

In addition to being one of the first studies examining the association between neural auditory processing and prelinguistic skills, our study makes a crucial contribution to the field by using LCS models. The LCS method explicitly models intra-individual change (Kievit et al., 2018; Petscher et al., 2016), whereas many commonly used methods such as Pearson correlations or ANOVA do not capture this time effect properly (Kievit et al., 2018; McArdle, 2009). Additionally, LCS models with latent variables become more conservative with an increasing rate of measurement error in data, which mitigates the risk of an inflated rate of type I errors caused by measurement error and therefore increases the reliability of the results (McArdle, 2009; Westfall and Yarkoni, 2016). In order to find the most robust associations between neural markers and subsequent language development, future studies should consider utilizing methods designed for analyzing longitudinal data instead of, or in addition to, the correlation analyses typically reported (Gueorguieva and Krystal, 2004; McArdle, 2009).

When interpreting our findings, some properties of the constructed models should be considered. Previous studies indicate that ITC scores for the Social, Speech and Symbolic subscale reflect both common (across subscales) and subscale-specific variation (Eadie et al., 2010; Määttä et al., 2016). In the current study, we used the three subscales to construct the latent variables ITC6 and ITC12, which captured the variance shared by the three subscales. Using latent variables allowed us to benefit from the advantages LCS models offer in dealing with measurement error (section 1, p. 4; section 4, p. 16). In line with the data on correlation between subscales (Tables 2a and 2b in section 2.5), the ITC latent loaded higher on the Symbolic than on the Speech subscale. This probably reflects the fact that different aspects of prelinguistic skills develop at different paces (Määttä et al., 2016; Sansavini et al., 2010). Nevertheless, all subscales were closely related to each other (Tables 2a and 2b). Accordingly, a one-factor solution shows a good fit to the ITC data at both 6 and 12 months of age, as well as in Model 1_{behav} where both time points and the change between the timepoints are included (Table 4 in section 3.2). We checked for measurement invariance of the ITC by fixing loadings of indicators (subscales) on the latent factor so that each indicator would have the same loading at both time points. Measurement invariance could not be established (see section 2.6.3 and Supplement 1), which suggests that the ITC questionnaire assessed slightly different constructs in 6- as compared to 12-month-olds. As the relative importance of different prelinguistic skills is likely to change with age (Määttä et al., 2016; Sansavini et al., 2010), the lack of measurement invariance was not surprising. To limit the number of tested models, we constructed LCS models only for the ERP components that showed significant associations ($p < 0.05$) in the preliminary Pearson correlations. Since Pearson correlations were done primarily for selection purposes, we refrain from further discussion concerning the components not included in the LCS models (N2, MMR_{dur}, and MMR_{vow}). One should also be cautious when comparing the results of the ERP components included in the LCS models (P1 and MMR_{freq}), as a proper comparison would require the components to be in the same model. In the current study, we constructed separate models for the components because we wanted to minimize the number of parameters in each model in order to ensure model stability.

A gender variable was included in all models to adjust for the fact that more girls than boys had missing values for ITC (see section 2.6.3). The observed trends of a larger P1 and a larger change in ITC in girls than in boys should be interpreted with caution, as these effects were absent in the models including only each of the relevant components (Supplement 2). To the final models we additionally added parental dyslexia and intervention status as control variables. Adding the control variables did not modify the main results (see Supplement 3 for details) indicating that within this framework parental dyslexia or intervention were not meaningfully associated with the relationship of the P1/MMR_{freq} and prelinguistic skills. Separate studies are needed to further investigate the relations between these background variables and neural auditory processing as well as language-related skills. In future studies, with even larger sample sizes, it would also be interesting to subgroup the data according to, for instance, the degree of parental dyslexia or the social environment of the child.

Our results support the idea that infant ERPs could be used to predict the subsequent development of language-related skills. The results also demonstrate the importance of assessing both concurrent and longitudinal relations between neural speech processing and language-related skills in order to profoundly understand the neural underpinnings of communicative development. Currently, it is still unclear whether ERPs could work as predictors of language-related skills at an individual level, and to what degree predictive mechanisms are the same for prelinguistic and linguistic outcomes. Further longitudinal studies are needed to disentangle the relations between neural auditory processing, prelinguistic, and linguistic skills, and to find the stimuli and ERP components most reliably predicting subsequent development.

Declarations of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100831.

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